

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Conf. No. 1859
Pascal PERRIAT et al. Art Unit: 1641
Application No.: 10/591,465 Examiner: Do, P. T.
Filed: 06/29/2007 Attorney Dkt. No.: 71247-0065
For: HYBRID NANOPARTICLES WITH LN₂O₃ CORE AND CARRYING BIOLOGICAL LIGANDS, AND METHOD OF PREPARATION THEREOF (AS AMENDED)

REQUEST FOR RECONSIDERATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action of January 3, 2011, a petition for a one month extension of time is requested and payment is made at the end of this filing.

Applicants request reconsideration of the final rejection of the claims. In review, claim 1 is rejected under 35 USC §103 based on the combination of Bazzi, Li, and Baumann. The rejection can be summarized as follows:

- 1) Bazzi teaches the claimed europium-doped nanoparticle but does not teach the claimed polysiloxane coating or the size limitations of claim 1.
- 2) Li allegedly teaches an europium-doped aluminum oxide that has a polysiloxane coating.
- 3) Since both Bazzi and Li teach material doped with europium, it would be obvious to employ the polysiloxane coating of Li on the particle of Bazzi.

- 4) Producing the polysiloxane coated nanoparticle of Bazzi does not produce the claimed size limitation.
- 5) Baumann teaches a polysiloxane coated particle with a polysiloxane coating thickness that overlaps that claimed.
- 6) The Examiner concludes that it would be obvious to employ the coating thickness of Baumann as the coating thickness for the Bazzi nanoparticle.

Applicants submit that the Examiner has committed a number of errors in the rejection and these errors mandate its withdrawal. The errors are discussed below under their respective heading.

The Examiner has erred in using the teachings of Li to modify Bazzi.

Critical to the Examiner's rejection is the stance that since each of Bazzi and Li teaches the use of europium as a doping element, it is permissible to look to the teachings of Li to modify Bazzi. The Examiner has committed error by using the common dopant of Bazzi and Li to support the rejection and ignoring the fact that it is the matrix material that controls the conditions for coating of materials not the dopant. As a result, one of skill in the art would not take the teachings of Li that employ an polysiloxane-coated aluminum framework or matrix and say that it would be obvious to coat the nanoparticles of Bazzi, which use a completely different framework, i.e., a rare earth oxide, with the coating material of Li.

The methods for obtaining a bonding between a shell and a core principally depend on the mechanical properties of the two constituents and not of the impurities or dopants contained in them. For instance, the reason responsible for the bonding of

polysiloxane with, on one hand, aluminum oxide framework and, on the other hand, a rare earth oxide such as gadolinium oxide has no relation with the fact that both oxides contain europium as a doping element.

The proof of this can be gleaned from the invention itself wherein it is demonstrated that grafting polysiloxane onto gadolinium oxide is done independently of the presence of europium. From an optical point of view, it is certain that the europium spectra which depend on the nature of the matrix should completely differ between both materials (from the relative intensities of the different emission peaks, the quantum yield, the life-time, etc.). This discrepancy arises from the size of Li's particles (preferentially some tenth or hundredth of nm) and that claimed in the present patent (preferentially, some nm). These particle sizes are completely different.

Indeed, in a nanoparticle, each atom is at a well defined distance from the surface and therefore has a specific atomic environment. On the contrary, in a macroscopic sample, each atom possesses the same neighbors. Then, in nanometer-sized samples, resonant jumps of excitation from europium to europium are no more possible so that the consequent concentration quenching is strongly reduced. The attachment herewith demonstrates this. The graph of the Attachment displays the emission for two Gd oxide samples differing in size. This gives then the proof that using a gadolinium matrix at the nanometer scale (here the core size is less than **3 nm**) is completely beneficial for obtaining considerably improved optical properties. Presently, this fact is certainly non known so that no assimilation can be made between the samples described by Li and the invention.

Baumann and Li are not in the field of Bazzi and not properly combined with Bazzi

Applicants have produced unexpected advances in the field of biological applications by providing improved hybrid nanoparticles that are sufficiently small in size but with improved stability against attack by an external aqueous medium, see paragraph [0031] of Applicants' published application. That is, in view of obtaining well properties for MRI, a lot of trials have been made to choose the more adequate thickness (resulting from a compromise between the dissolution of gadolinium cations, an accessibility of the water protons and an overall size of the architecture leading to particles elimination via renal route). Also trials have been made to choose the more adequate composition (also here a compromise between porosity and mechanical strength was made). In this regard, the invention defines a new composition that is not the same or similar to those already patented or described in literature.

The Examiner's position that the invention is obvious simply because it resembles other conditions already claimed or published is not correct. First, arriving at the invention was not something that was done without great effort; Applicants have expended much time and effort to arrive at the invention. Further, the invention has been described in well known journals, as pointed out in the last response, which is further evidence of the great effort expended to arrive at the invention. What Applicants have done is to create a hybrid nanoparticle that is not the same or similar to the prior art and is one that provides significant advantages in the imaging field, particularly with respect to the MRI properties. The prior art, as in Li, does not even require a shell of polysiloxane. Further, the prior art does not recognize the importance

of the control of the overall size of the particle, in that Li's core/polysiloxane structure is not one that has a total size < 5 nm. This fact is that both a layer of polysiloxane and a total size that does not overcome 5 nm is not found in the teachings of Li and Baumann. It is imperatively required by scientific and new arguments concerning the design of a multifunctional particle that possesses a renal excretion. The reason is that, on one hand, Baumann and Li and, on the other hand, the invention, are not IN THE SAME ART.

If it would have been the case, Baumann and Li would have obviously claimed a particle smaller than 5 nm since this size is the well-known limit that separates renal and hepatic elimination. To one of ordinary skill in the art of designing particles for multi-imaging and therapy, it is obvious that the natures of the art of Baumann and Li are completely different from the art concerned by the invention and one of skilled in the art would not look to these patents to modify Bazzi.

The Examiner's picking of a coating thickness based on Baumann to satisfy the failure of Bazzi and Li to teach the claimed coating size lacks the proper factual underpinnings.

The Examiner errs by concluding that it would be obvious to specify the size of the polysiloxane coating of Bazzi because Baumann teaches a polysiloxane coating that overlaps that which is claimed. In the rejection, the Examiner says that it would be obvious to coat the particles of Bazzi and Li in the manner of the invention "in order to completely coat the particles." The Examiner also states that that one "would have a reasonable expectation of success in combining the teachings of Bazzi, Li, and Baumann

since they all teach obtaining nanoparticles with an average size of 5 nm."

Applicants ask what is the reasonable expectation of success in the statement by the Examiner?

When Li and Baumann teach about the coating of polysiloxane, they do not teach the same lesson but argue in different domains of the materials science. When Baumann defines a polysiloxane thickness, this concerns something that is completely different from the coating of a particle of the invention or even Li or Bazzi. Therefore, why would one skill in the art of the elaboration of particles for medical purposes look to the scale range given by Baumann which deals with a completely different application? There is no reason or expectation of success given the fact that Baumann is far afield of Bazzi or Li. The mere fact that a polysiloxane thickness exists in the prior art does not mean that such would be selected for the thickness of the coating of the Bazzi particle.

Applicants also submit that the reasoning of "completely coat the particles" is one generated by the Examiner not the prior art. Moreover, completely coating the particles does not mean that the coating thickness sized is taught to be controlled. Therefore, even if the Examiner were correct to say that the prior art wants the particles to be completely coated; this is not the same as the control of the particle size and coating size of the invention. This complete coating of the particles reasoning cannot lead to the invention and a *prima facie* case of obviousness is not established using this reasoning.

Li does not teach how to make the product and therefore, a *prima facie* case

of obviousness is not established.

While a product is claimed, the Examiner's reasoning for making the rejection must also include the ability to make the claimed product. It is well settled that in order to render an apparatus or method obvious, the prior art must enable one of skill in the art to make and use the apparatus or method. *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989). As a corollary to this, the Examiner is permitted to shift the burden of demonstrating that the prior art is not enabling if the prior art would disclose a composition or device that would be similar to that claimed. *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005).

In this present instance, the teachings of Li are not even remotely similar to that of the invention to support a stance that the ability to make the claimed coating and size limitations on a rare earth oxide nanoparticle is present in Li. This means that the Applicants do not have to rebut this presumption with some evidence; the presumption is in error.

In the rejection, the Examiner says that it would be obvious to coat the nanoparticles of Bazzi with the polysiloxane of Li. The Examiner assumes that the manner of doing so is also taught so that the artisan is capable of producing the hybrid nanoparticle of claim 1.

Applicants submit that Li does not teach how to coat the Bazzi particle such that the mean thickness as claimed can be obtained.

Li clearly does not teach the method that is employed by the inventors to obtain the coating. Therefore, the manner in which Li teaches coating of the aluminum oxide framework with the polysiloxane must be examined to determine whether Li's methods

are capable of producing the claimed coating.

The method of coating the aluminum oxide of Li is not in the least similar to that employed by the invention. This is evident when comparing the sol-gel technique described in the specification to Li. Li describes a process of mixing a coating reagent with the particles, mixing at an elevated temperature, centrifuging, and then heating in a microwave. It should be noted again that the coating of Li is optional so that its importance is not critical to the invention of Li.

It is also important to note that Li never says what the coating thickness is or that its control is important.

The question raised here is whether Li provides a teaching concerning how the claimed coating would be produced. Applicants submit that Li does not teach one of skill in the art how to produce the claimed coating. There are number of factors that affect the coating and the size of a coating as follows:

- 1) the composition surface. That is, the composition surface modifies the physic-chemical conditions of the sol-gel technique used in the present invention and, as a result, the nucleation processes and the homogenous or non-homogenous character of the coating obtained by such a process.
- 2) Non-specific nucleation and non specific cross linking. It is essential to the invention that non specific nucleation and non cross linking between nanospheres occurs in order to keep the desired small size.
- 3) the sol gel process used to make the coating.

4) Heating of the coated particle. As previously argued, in the case of biological applications, for insertion of organic fluorophore and in order to avoid agglomeration, the nanoparticles of the invention cannot be heated, as is required in Li.

Again, Li does not even speak of control of the size of the coating on the aluminum oxide framework. Moreover, there is no recognition of the factors mentioned above or that they can affect the size of the particles, including the coating size. The Examiner does not have an objective basis to conclude that the processing of Li would lead to the controlled nanoparticle. How does the Examiner arrive at the conclusion that the size of the coating made by Li can be controlled to meet the claim limitations. Li offers no guidance in this regard. Therefore and despite the Examiner's assumption that the claimed product with its limitations on the size of the core nanosphere and size of the coating thereon, the prior art, in fact, does not teach one of skill in the art that the size of the coating of Li is important nor how to control said size. Without this teaching, one of skill in the art does not know how to control the size of the coating of Li so as to control the size of the coated nanoparticle. Thus, the rejection of claim 1 is not valid and must be withdrawn.

The Examiner cannot rely on an optimization theory since the size of the coating in Li is not even recognized as a variable that needs to be controlled. As the Examiner knows, optimization of a variable, in this case, the size of the coating, requires that the variable is one that is recognized to be optimized. This recognition is absent in Li so that an allegation that the control of the size of the coating in Li is nothing more than an optimization cannot be made.